Pancreatic Cancer: Alarm for Survival

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ABSTRACT

Pancreatic cancer is one of the deadliest and a highly aggressive cancer. Its incidence and mortality are highest in developed countries. However, in Asia-Pacific region, the incidence and mortality rate of pancreatic cancer are also on increasing trend nowadays. Pancreatic cancer incidence rates increase with older age, the highest in the 7th and 8th decades. Clinical presentation of pancreatic cancer are usually non-specific, largely dependent on tumour size and location, with most patients experience symptoms already late in the disease. Computed tomography is considered the method of choice for diagnosis and staging of pancreatic cancer. Management for pancreatic cancer include surgical resection, radiotherapy, chemotherapy. Only surgical resection considered the potentially curative treatment for pancreatic cancer. Unfortunately, a lot of patients present with disease that is not surgically resectable. Prognosis for pancreatic cancer is very poor, despite surgery in resectable patients. The overall five-year survival rate is about less than 5%

Keywords: *pancreatic cancer, diagnosis, management*

ABSTRAK

Kanker pankreas merupakan salah satu tipe kanker yang mematikan dan sangat agresif. Insidens dan mortalitas dari kanker pankreas tertinggi adalah dari negara maju. Akan tetapi, di wilayah Asia Pasifik, angka insidens dan mortalitas dari kanker pankreas juga dalam tren meningkat sekarang ini. Insiden kanker pankreas meningkat dengan bertambah tuanya umur, paling tinggi di dekade ke 7 dan 8. Presentasi klinis dari kanker pankreas biasanya non spesifik, tergantung dari ukuran dan lokasi tumor, dengan kebanyakan pasien mengalami gejala sudah di stadium lanjut. Computed tomography dianggap metode pilihan untuk mendiagnosis dan menentukan stadium dari kanker pankreas. Pengobatan kanker pankreas mencakup bedah reseksi, radioterapi dan kemoterapi. Hanya tindakan bedah reseksi yang dianggap berpotensial untuk menyembuhkan kanker pankreas. Sayangnya, kebanyakan pasien datang dengan penyakit kanker pankreas yang sudah tidak bisa direseksi. Prognosis dari kanker pankreas sangat jelek, meskipun pasien dengan kanker pankreas yang bisa direseksi. Angka harapan hidup 5 tahun hanya kurang dari 5%.

Kata kunci: *pancreatic cancer, diagnosis, management*

INTRODUCTION

According to GLOBOCAN 2012, pancreatic cancer causing more than 331,000 deaths per year, which ranked as seventh leading cause of cancer death in both sexes together. Pancreatic cancer also ranked the 12th most common cancer in the world with 338,000 new cases. The highest incidence and mortality rates of pancreatic cancer are found in developed countries. In Asia Pacific region, the mortality rate of pancreatic cancer are on increasing trend nowadays.[2] The incidence rates of pancreatic cancer for both sexes increase with age, the highest in the 7th and 8th decades of life. There are many condition that considered as risk factors for pancreatic cancer. The risk factors are divided into modifiable and non-modifiable. Modifiable risk factors include smoking, obesity, alcohol and dietary factors, while non-modifiable risk factors include increasing age, familial cancer syndromes, race, hereditary, diabetes mellitus, and chronic pancreatitis.[3]

The survival rate of pancreatic cancer is very poor; the overall 5-year survival is about less than 5%. Surgical resection is the only potentially curative treatment of choice for pancreatic cancer. The majority of patients are diagnosed at an advanced stage where surgical resection is not an option for treatment, hence the low survival rate. Despite improvements in imaging, surgical techniques and chemotherapy, overall survival has not improved in the past few decades.[1]

Clinical Presentation

The clinical presentation of patients with pancreatic cancer are usually non-specific, it largely depends on the size and location of the tumor. Pancreatic cancer location approximately 60-70% in the head of pancreas, 20-25% in the body and tail of pancreas, dan the remaining 10-20% diffusely involve the pancreas. Symptoms of pancreatic cancer include jaundice, abdominal pain, weight loss, steatorrhoea, and new onset diabetes.[4]

Diagnostics

Pancreas protocol CT is the gold standard for diagnosis and staging pancreatic cancer. The pancreatic protocol CT consists of dual-phase scanning using intravenous and oral contrast agents. It is the most widely used modality for diagnosis and staging of pancreatic cancer due to the fairly wide availability. CT can be used to assess potential vascular involvement and metastases.[5,6] Although the widely used of CT for diagnosis of pancreatic cancer, MRI can also play an important role. MRI have more superior soft tissue contrast that can detect small, non-countour deforming tumors which may not be seen on CT. MRI and CT have similar performance for staging of pancreatic cancer. In some cases, MRI improves detection of hepatic metastases and characterization of CT-indeterminate liver lesions.[7]

Another modality used in the diagnosis of pancreatic cancer is endoscopic ultrasound (EUS). EUS with Fine Neddle Aspiration (FNA) can help secure tissue for cytologic diagnosis which made it essential for diagnosing pancreatic cancer. EUS can provide staging of suspected or proven pancreatic cancer, and cytological/histological proof of unresectable pancreatic cancer.[8] Although EUS is a minimally invasive procedure, it is considered a safe procedure with low complication rates. Complications of EUS procedure include bleeding, pancreatitis, perforation, and rarely tumor seeding after EUS-FNA.[9]

Staging

The American Joint Committee on Cancer (AJCC) 8th edition staging system for pancreatic cancer is shown Table 1. This new staging system different from the previous 7th edition. The T category is revised from descriptive to size-based definitions. Another change, resectability is removed from the T4 category because the definition of resectability is not consistent among institutions and evolves with advances in surgical technique.[10]

Table 1. American Joint Committee on Cancer (AJCC) 8th edition staging system for pancreatic cancer

Tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ (includes PanIN III)		
T1	Maximum tumor diameter ≤ 2 cm		
T2	Maximum tumor diameter >2, ≤4 cm		
T3	Maximum tumor diameter >4 cm		
T4	Tumor involves the celiac axis, common hepatic artery or the superior mesenteric artery		
Lymph node metastases (N)			
N0	No regional lymph node metastasis		
N1	Metastasis in 1–3 regional lymph nodes		
N2	Metastasis in ≥ 4 regional lymph nodes		
Distant metastases (M)			
M0	No distant metastasis		
M1	Distant metastasis		
American Joint Comittee on Cancer (AJCC) staging			
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1-3	N1	M0
Stage III	Any T	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Reprinted from American Joint Committee on Cancer (AJCC) 8th edition

TREATMENT

Resectable

Surgical resection is a potentially curative treatment for pancreatic cancer, but only 15–20% of patients present with a resectable disease.[11] Patients who have localized disease with no metastases, good performance status and no significant comorbidities are a good candidate for surgical resection. The classic surgery for resection is a pancreaticoduodenectomy, also known as Whipple procedure.[12] Pancreatic cancer patients who undergo surgical resection is recommended to be given adjuvant chemotherapy.[13] ESPAC-4 trial showed that patients with resected pancreatic cancer who were given adjuvant combination of gemcitabine and capecitabine had improve overall survival compared with only gemcitabine (OS: 28 months vs. 25.5 months; HR for death 0.82; 95% CI 0.68–0.98).[14] There is still no recommendation to giving neoadjuvant chemotherapy in resectable pancreatic cancer because no significant improvement in overall survival.[15]

Borderline Resectable

Borderline resectable pancreatic cancer have a higher risk for positive margin after resection. Therefore, neoadjuvant therapy recommended to be given before surgical resection of borderline resectable pancreatic cancer. A study using FOLFIRINOX followed by capecitabine based chemoradiation for borderline resectable pancreatic cancer showed a successful pancreatectomy (68%) with negative margins resection rates (93%).[16]

Locally Advanced

Patients with locally advanced pancreatic cancer who underwent surgical resection usually had a poor prognosis due to high rates of margin positivity after surgical resection. Systemic chemotherapy is the preferred treatment for locally advanced pancreatic cancer. A systematic review and meta analysis study using FOLFIRINOX as systematic chemotherapy showed a median overall survival longer (24.2 months) compared to gemcitabine (6-13 months). The study also showed about 28% patients were able to underwent surgical resection of tumour and 78% of them had negative margin resection.[17] Chemotherapy in this situation is never curative, and its palliative benefit must be balanced against its potential toxic side effects. Despite treatment, the survival outcomes remain poor.[18]

Endoscopic Ultrasound (EUS) Interventional Therapy

EUS interventional therapy in pancreatic cancer management is emerging. Many applications using EUS include fiducials placement, brachytherapy, fine needle injection (FNI) and radiofrequency ablation (RFA). Fiducial are inert radiopaque spheres, coils, or cylindricals that are implanted inside or adjacent to the tumor in order to aid image-guided radiation therapy (IGRT). EUS-guided fiducials placement first reported by Pishvaian *et al* in case series of 13 patients where technical success achieved in 94% patients.[19] Followed by several case series with technical success more than 90%.[20-22]

EUS-brachytherapy apply the insertion of a radioactive seed (iodine-125, iridium-192, and palladium-103) directly into the pancreatic tumor. Brachytherapy still need more larger studies for evaluation. Studies done showed EUS-brachytherapy safe, feasible and have benefit in pain control.[23-25]

EUS-FNI apply direct injection of therapeutic agents into pancreatic tumors. EUS-FNI is safe and feasible, but not yet show long term efficiency.[26-27] EUS-RFA role in management of pancreatic cancer had been showed in recent studies. A study by Song et al demonstrated safety and feasibility of EUS-RFA in patients with unresectable pancreatic cancer. Technical success in this study was achieved 100% however overall survival can't be assessed.[28]

CONCLUSION

Pancreatic cancer still considered one of the deadliest cancer types. Survival rate of this disease is very poor. There are many diagnostics modality for diagnosing pancreatic cancer but early diagnosis of pancreatic cancer is still difficult. One of the factor is because patients only experience symptoms of pancreatic cancer late in the course of the disease. Despite treatment, pancreatic cancer high aggressiveness and resistance to modern chemo-radiotherapy are associated with low rates of long-term survival. Studies using EUS as interventional therapy showed promising results. More larger studies are needed to establish the role of these procedures in the treatment of pancreatic cancer. There are no screening recommendations for pancreatic cancer, so primary prevention is of utmost importance.

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